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The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies

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Abstract Since the 1990s, the International Union of Immunological Societies (IUIS) PID expert committee (EC), now called Inborn Errors of Immunity Committee, has published every other year a classification of the inborn errors of

immunity. This complete catalog serves as a reference for immunologists and researchers worldwide. However, it was unadapted for clinicians at the bedside. For those, the IUIS PID EC is now publishing a phenotypic classification since 2013,

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which proved to be more user-friendly. There are now 320 single-gene inborn errors of immunity underlying phenotypes as diverse as infection, malignancy, allergy, auto-immunity, and auto-inflammation. We herein propose the revised 2017 phenotypic classification, based on the accompanying 2017 IUIS Inborn Errors of Immunity Committee classification.

Keywords Primary immunodeficiencies · Classification · Phenotypic · IUIS · Inborn errors of immunity

Human primary immunodeficiency diseases (PID) comprise 330 distinct disorders with 320 different gene defects listed [1]. Long considered as rare diseases, recent studies tend to show that they are more common than generally thought, if only by their rapidly increasing number [2, 3]. The International Union of Immunological Societies (IUIS) PID expert committee proposed a PID classification since 1999 [1], which facilitates clinical research and comparative studies worldwide; it is updated every other year to include new disorders or disease-causing genes. This classification is organized in tables, each of which groups PIDs that share a given pathogenesis. As this catalog is not adapted for use by the clinician at the bedside, the now called Inborn Errors of Immunity Committee proposed since 2013 a phenotypic complement to its classification [4]. Moreover, a smartphone application has been published, based on the 2015 phenotypic classification [5]. As the number of inborn errors of immunity is quickly increasing,

Fig. 1 Immunodeficiencies affecting cellular and humoral immunity. **a** Severe combined immunodeficiencies defined by T cell lymphopenia. **b** Combined immunodeficiencies. * T cell lymphopenia in SCID is defined by CD3+ T cells < 300/μL. AD: autosomal dominant transmission; ADA: adenosine deaminase; Ag: antigen; AR: autosomal recessive transmission; β2m: β2-microglobulin; Bc: B cells; CBC: complete blood count; CD: cluster of differentiation; CVID: common variable immunodeficiency; def: deficiency; EBV: Epstein Barr virus; HHV8: human herpes virus 8; HIGM: hyper IgM syndrome; HPV: human papillomavirus; Ig: immunoglobulins; MHC: major histocompatibility complex; NI: normal; NK: natural killer; SCID: severe combined immunodeficiency; Tc: T cells; TCR: T cell receptor; Treg: regulatory T cells; XL: X-linked transmission

and at an even faster pace since the advent of next-generation sequencing, this phenotypic classification requires revision at the same pace as the classical IUIS classification.

Here, we present an update of these figures (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9), based on the accompanying 2017 report in inborn errors of immunity. We included all diseases included in the 2017 update of the IUIS classification [1] and split some categories in two parts to ease the lecture. An algorithm was assigned to each of the nine main groups of the classification and the same color was used for each group of similar conditions. Disease names are presented in red and genes in bold and italics. Mode of inheritance is expressed when adequate; if not expressed, the default mode of transmission is autosomal recessive. Clinical features that point to several diseases are presented in italics before the disease names.

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I. Immunodeficiencies affecting cellular and humoral immunity.

(a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia*.

CD19 NL : SCID T- B+		CD19 ↓ : SCID T-B-	
SCID T-B+NK-	SCID T-B+NK+		SCID T-B-NK+
XL, CD 132- <i>γc deficiency.</i> IL2RG	IL7Rα . IL7R No γ/δ T cells: CD3δ. CD3D CD3ε. CD3E CD3ζ . CD247 NI γ/δ T cells : CD45 def. PTPRC	Coronin-1A def . CORO1A Detectable thymus Winged helix def. FOXN1. Severe infections; abnormal thymic epithelium; congenital alopecia, nail dystrophy, neural tube defect.	Microcephaly ? Yes No - With facial dysmorphism: DNA ligase IV def . LIG4 CERNUNNOS /XLF def. NHEJ1. Radiation sensitive - Without facial dysmorphism: DNA PKcs def. PRKDC Radiosensitivity RAG 1/2 def. (RAG1/ RAG2) DCLRE1C def. DCLRE1C (ARTEMIS). Radiosensi- bility
AR, CD 132+ JAK-3 def. JAK3		ADA def . ADA Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects Reticular dysgenesis. AK2 Granulocytopenia, Thrombocytopenia deafness.	

I. Immunodeficiencies affecting cellular and humoral immunity

(b) Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency

Low CD4: MHCII Expression ?	Low CD8	Low Bc:	Ig : often NL	Ig Low	Normal Ig but Poor Specific Antibody response
Absent : MHC-II def. RFXANK, CIITA, RFX5, RFXAP Diarrhea, respiratory infections, liver/biliary tract disease	Present: XL MAGT1 def. MAGT1. AR, LCK def. LCK. Immune dysregulation, autoimmunity. Low Treg, restricted T cell repertoire, poor TCR signaling; AD :UNC119 def. UNC119	DOCK8 def. DOCK8. Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer ,diathesis. High IgE, Low IgM, eosinophilia. Low NK with poor function. Low CD27+ memory Bc Poor peripheral Bc tolerance. MS1 def. STK4. Intermittent neutropenia; bacterial, viral (HPV), candidal infections; EBV lymphoproliferation; autoimmune cytopenias; lymphoma; congenital heart disease. Low T and B. High Ig. Low terminal differentiated effector memory cells, low naive Tc, poor proliferation.	CD3γ def. CD3G TCR low. RHOH def. RHOH. HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naive T cells, restricted repertoire, poor proliferation to CD3. TCRa def. TRAC. Recurrent viral, bacterial, fungal infections; immune dysregulation and autoimmunity; diarrhea. Absent TCRαβ; all Tc are γδ; poor proliferation. BCL11B deficiency. BCL11B. AD. Congenital abnormalities: neonatal teeth, dysmorphic facies; absent corpus callosum; neurocognitive deficits. Tc : Low, poor proliferation. OX40 def. OX40. Kaposi's sarcoma, impaired immunity to HHV8. Low memory Bc. Tc : low Ag specific memory CD4+.	DOCK2 def. DOCK2. Low Tc; NL NK but defective function. Poor interferon responses in hematopoietic and non-hematopoietic cells. IgG NL or low; poor antibody responses. CARD11 deficiency (LOF). CARD11. <i>Pneumocystis jirovecii</i> pneumonia, bacterial & viral infections .Ig: Absent/low. Tc: NL number, poor proliferation BCL10 def. BCL10. Recurrent bacterial and viral infections, candidiasis, gastroenteritis. Low memory T and Treg cells, poor Ag and anti-CD3 prolif. Decreased memory and switched Bc IKBKB def. IKBKB. Recurrent bacterial, viral and fungal infections. Opportunistic infections. Bc : poor functions. absent Treg and γδ T cells; impaired TCR activation. ICOS def. ICOS. Autoimmunity, gastroenteritis, granulomas (CVID). TFRC deficiency. TFRC. Neutropenia, thrombocytopenia. Bc: NI number, low memory Bc. Tc: NI number, poor proliferation . RelB deficiency. RELB. Tc: poor diversity, poor function CD40 ligand def. (CD154). XL, CD40LG. or CD40 def. AR, CD40. Opportunistic infections, biliary tract and liver disease, <i>Cryptosporidium</i> . HIGM. Neutropenia, thrombocytopenia, hemolytic anemia, IgM normal or high, other Ig isotypes low. Bc: sIgM*, IgD* cells present, absent sIgG*, IgA* and IgE* cells. Tc: NL to low.	IL21R def. IL21R. Recurrent infections; <i>Pneumocystis</i> , <i>Cryptosporidium</i> . Tc: low cytokine production; poor antigen proliferation. MALT1 def. MALT1. Bacterial, fungal and viral infections. Impaired Tc proliferation and antibody response
CD8 def . CD8A Maybe asymptomatic. CD8 Absent. NI MHC I on lymphocytes. ZAP70 def. ZAP70 May have immune dysregulation, autoimmunity. NI Ig. CD4: Low fonction		IL21 def. IL21. Severe early onset colitis. Low IgG. Tc : NL / low fonction. NIK def. MAP3K14. Bacterial, viral and <i>Cryptosporidium</i> infections. Low NK and Ig levels. Low switched memory Bc. Tc : Ag poor proliferation	LAT def . LAT. Adenopathy, splenomegaly, autoimmunity. High Ig . T and B : NL to low		
Absent MHC I on lymphocytes. MHC-I def . TAP2, TAP1 or TAPBP Vasculitis, pyoderma gangrenosum. NI Ig. B2M Sinopulmonary infections, cutaneous granulomas. NI Ig. Hypoprotidemia. Absent β2m associated proteins MHC-I, CD1a, CD1b, CD1c.		Moesin def. MSN. XL, Recurrent infections with bacteria, varicella; neutropenia. Low Ig over time. Tc: defective migration, proliferation.			

IIa. CID with associated or syndromic features

Congenital thrombocytopenia	DNA Repair Defects other than those listed in Table1: Karyotype	Immuno- osseous dysplasias	Thymic Defects with Additional Congenital Anomalies
<p>XL: Wiskott Aldrich Sd . WAS (LOF). XL thrombocytopenia is a mild form of WAS. Recurrent bacterial and viral infections; bloody diarrhea; eczema; lymphoma; autoimmune disease; IgA nephropathy; vasculitis. Small platelets; Decreased IgM. Low antibody to polysaccharides; often increased IgA and IgE. NI Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.</p> <p>AR: WIP deficiency. WIPF1. Recurrent bacterial and viral infections; eczema; bloody diarrhea . WAS protein absent. +/- small platelets; increased IgE. Bc : NI to low. Tc: Reduced; defective lymphocyte responses to anti-CD3.</p> <p>AR: ARPC1B deficiency. ARPC1B. Recurrent invasive infections, colitis, vasculitis. Mild thrombocytopenia, normal sized platelets; autoantibodies (ANA, ANCA); eosinophilia; defective Arp2/3, filament branching. High IgA and IgE.</p>	<p>Ataxia telangiectasia. ATM: Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein; increased radiosensitivity, chromosomal instability and translocations. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Tc : Progressive decrease, abnormal proliferation to Mitogens.</p> <p>Nijmegen breakage sd. NBS1. Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Bc: Variably reduced. Tc: progressive decrease.</p> <p>Bloom sd. BLM. Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability. Low Ig.</p> <p>PMS2 def. PMS2. Café-au-lait spots ; lymphoma, colorectal carcinoma, brain tumors. HIGM and abnormal antibody responses. Reduced Bc, switched and non-switched.</p> <p>Immunodeficiency with centromeric instability and facial anomalies. ICF1.DNMT3B; ICF2:ZBTB24; ICF3:CDCA7; ICF4:HELLS. Facial dysmorphism; macroglossia; bacterial/opportunistic infections; malabsorption; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16; no DNA breaks. Ig: Hypogammaglobulinemia; Tc and Bc: decreased or NI.</p> <p>MCM4 def. MCM4. Viral infections:EBV,HSV,VZV.Short stature.Bc lymphoma; Adrenal failure; NKc low number and function.</p> <p>RNF168 def. RNF168. Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity (= Riddle Sd). Low IgG or IgA.</p> <p>POLE1 (Polymerase ϵ subunit 1) deficiency . POLE1. Recurrent respiratory infections; meningitis; facial dysmorphism, livido, short stature (FILS syndrome). Low IgM, lack of antibody to PPS. Low memory Bc. Decreased Tc proliferation.</p> <p>POLE2 (Polymerase ϵ subunit 2) deficiency. POLE2. Recurrent infection, systemic BCG infections, autoimmunity (type 1 diabetes, hypothyroidism), facial dysmorphism; Low Ig; Very low Bc. Lymphopenia, lack of TRECS, absent proliferation of antigens.</p> <p>NSMCE3 deficiency. NSMCE3. Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage; radiation sensitivity. Ig: Decreased Ab responses to PPS, normal IgG, IgA, elevated IgM. Tc : Number decreased, poor response to mitogens and antigens.</p> <p>ERCC6L2 (Hebo deficiency). ERCC6L2. Facial dysmorphism; microcephaly, bone marrow failure. Low Bc, NI Ig. Lymphopenia.</p> <p>Ligase I deficiency . LIG1 Recurrent respiratory infections; growth retardation; sun sensitivity; lymphoma; radiation sensitivity. Low IgA and IgG. Reduced antibody responses. Lymphopenia, decreased mitogen response.</p> <p>GIN51 def. GINS1. IUGR. Neutropenia, NK cells very low. Tc: and Bc low or normal. High IgA, Low IgG and IgM.</p>	<p>Cartilage Hair Hypoplasia. RMRP. Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: Normal or reduced. Tc: Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation.</p> <p>Schimke sd. SMARCA1 Short stature, spondylo-epiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure. Tc: Decreased.</p> <p>MYSM1 deficiency. MYSM1. Short stature, congenital bone marrow failure, myelodysplasia, Skeletal anomalies; cataracts; developmental delay. Affects granulocytes. Bc: immature. Tc: lymphopenia, reduced naive Tc. Hypogammaglobulinemia.</p> <p>MOPD1 Deficiency. RNU4ATAC. Recurrent bacterial infections, lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. Ig: NL specific antibodies variably decreased.</p> <p>EXTL3 Deficiency. EXTL3. Platyospondyly, kyphosis, variable skeletal dysplasias, developmental delay Ig: variably decreased. Tc: reduced.</p>	<p>AD. Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability . Ig : Normal or decreased. Tc: Decreased or NI : DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS. TBX1 deficiency . TBX1 + Renal disease, deafness. Chromosome 10p13-p14 deletion Syndrome. 10p13-p14DS.</p> <p>AD. CHARGE sd. CHD7, SEMA3E. Coloboma, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation; some are SCID-like and have low TRECs. Ig: Normal or decreased. Tc: Decreased or normal; response to PHA may be decreased</p>

Fig. 2 a, b CID with associated or syndromic features. Ab: antibody; AD: autosomal dominant transmission; ANA: anti-nuclear antibodies; ANCA: anti-neutrophil cytoplasm antibodies; AR: autosomal recessive transmission; Bc: B cells; BCG: Bacillus Calmette-Guerin; BCR: B cell receptor; CD: cluster of differentiation; CMV: cytomegalovirus; CNS: central nervous system; def: deficiency; DNA: deoxyribonucleic acid; DKC: dyskeratosis congenita; EDA: anhidrotic ectodermal dysplasia; GOF: gain-of-function; HIES: hyper IgE syndrome; FILS: facial

dysmorphism, immunodeficiency, livedo and short stature; ID: immunodeficiency; Ig: immunoglobulins; IUGR: intrauterine growth retardation; LOF: loss-of-function; MDS: myelodysplasia; NI: normal; NK: natural killer; PHA: phytohemagglutinin; PPS: polysaccharides; SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells; TCR: T cell receptor; TREC: T cell receptor excision circle; XL: X-linked transmission

IIb. CID with associated or syndromic features				
Hyper-IgE syndromes (HIES) AD-HIES (Job sd). <i>STAT3</i> , LOF. Distinctive facial features (broad nasal bridge); bacterial infections (boils and pulmonary abscesses, pneumatoceles) due to <i>S. aureus</i> , <i>Aspergillus</i> , <i>Pneumocystis jirovecii</i> ; eczema; mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth; aneurysm formation <i>Ig</i> : Elevated <i>IgE</i> ; specific antibody production decreased. Bc: Normal; reduced switched and non-switched memory Bc; BAFF expression increased. Tc: NI overall; Th-17 and T-follicular helper cells decreased. Comel Netherton sd. <i>SPINK5</i> ; Congenital ichthyosis, bamboo hair; atopic diathesis; increased bacterial infections. Elevated <i>IgE</i> and <i>IgA</i> ; Other <i>Ig</i> : variably decreased. Bc: Switched and non-switched Bc are reduced. PGM3 deficiency. <i>PGM3</i> . Severe atopy; autoimmunity; Immunosseous dysplasias. Recurrent pneumonia, recurrent skin abscesses, bacterial and viral infections; cognitive impairment; hypomyelination. <i>Ig</i> : NI or elevated. Elevated <i>IgE</i> ; eosinophilia. Reduced B and memory Bc. CD8 and CD4 Tc may be decreased.	Dyskeratosis congenita (DKC) Myelodysplasia, defective telomere maintenance Exclude other causes: Fanconi anemia, Blackfan-Diamond Dyskeratosis congenita. IUGR, microcephaly, nail dystrophy, sparse scalp hair and eyelashes; poikiloderma or abnormal skin pigmentation; palmar hyperkeratosis; premalignant oral leukoplakia; pancytopenia; +/- recurrent infections. A severe phenotype with developmental delay and cerebellar hypoplasia known as Hoyeraal-Hreidarsson Syndrome (HHS) may occur in some patients. <i>Ig</i> and Bc: variable. DKC1 : XL, Bc and Tc: Progressive decrease. NOLA2 (NHP2) , NOLA3 (NOP10) : AR, Tc: Decreased. RTKL1 : AD/AR, Tc: Decreased. TERC , TINF2 : AD, Tc: variable. TERT , TPP1 : AD/AR, Tc: variable. DCLRE1B/ SNM1/APOLLO, PARN, WRAP53 : AR, Tc: variable. COATS plus Sd. Intracranial calcification, abnormal telomeres, IUGR, gastrointestinal hemorrhage due to vascular ectasia, hypocellular bone marrow. pancytopenia STN1 : premature aging, CTC1 : sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia SAMD9 . AD. SAMD9 (GOF): IUGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen SAMD9L . AD. SAMD9L (GOF): Cytopenia, predisposition to MDS with chromosome 7 aberrations and progressive cerebellar dysfunction	Defects of Vitamin B12 and Folate Metabolism: <i>Megaloblastic anemia, Ig: decreased.</i> Transcobalamin 2 deficiency. TCN2 . pancytopenia, if untreated for prolonged periods results in intellectual disability. Deficiency causing hereditary folate malabsorption. SLC46A1 . if untreated for prolonged periods results in intellectual disability Methylene-tetrahydrofolate dehydrogenase 1 deficiency. MTHFD1 . Recurrent bacterial infection, <i>Pneumocystis jirovecii</i> , neutropenia, seizures, intellectual disability, folate-responsive, poor antibody responses to conjugated polysaccharide antigens. Low Bc.	Anhidrotic Ectodermodyplasia with ID <i>Anhidrotic ectodermal dysplasia, various infections (bacteria, mycobacteria, viruses and fungi), colitis, variable defects of skin, hair and teeth.</i> NEMO deficiency. IKBKG (NEMO) . XL, monocyte dysfunction. <i>Ig</i> decreased, some with elevated <i>IgA</i> , <i>IgM</i> , poor specific antibody responses, absent antibody to polysaccharide antigens. Bc: NI, Low memory and isotype switched Bc. Tc: NI/decreased, TCR activation impaired. EDA-ID due to IKBA GOF mutation. NFKBIA (IKBA) . AD Tc and monocyte dysfunction Decreased <i>IgG</i> and <i>IgA</i> , elevated <i>IgM</i> , poor specific antibody responses, absent antibody to polysaccharide antigens. Normal Bc numbers, impaired BCR activation, low memory and isotype switched Bc. Normal total Tc, TCR activation impaired.	Others Purine nucleoside phosphorylase deficiency. PNP . Autoimmune hemolytic anemia, neurological impairment. Hypouricemia. <i>Ig</i> : NI/Low. Bc: NI. Tc: Progressive decrease ID with multiple intestinal atresias. TTC7A . Bacterial (sepsis), fungal, viral infections, multiple intestinal atresias, often with intrauterine polyhydramnios and early demise, some with SCID phenotype. Markedly decreased <i>IgG</i> , <i>IgM</i> , <i>IgA</i> . Bc: NI/low. Tc: Variable/absent, low TRECs. Hepatic veno-occlusive disease with immunodeficiency (VODI). SP110 . Hepatic veno-occlusive disease, <i>Pneumocystis jirovecii</i> pneumonia, CMV, candida, thrombocytopenia, hepatosplenomegaly, cerebrospinal leukodystrophy. Decreased <i>IgG</i> , <i>IgA</i> , <i>IgM</i> , absent germinal centers and tissue plasma cells. Decreased memory Bc. Decreased memory Tc. Vici syndrome. EPG5 . Agenesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, intellectual disability, microcephaly, CMC. <i>Ig</i> : Decreased <i>IgG2</i> . Bc: Defective. Profound depletion of CD4+ cells. <i>Bacterial infections, autoinflammation, amylopectinosis. Bc: NI, decreased memory Bc.</i> HOIL1 deficiency. HOIL1 (RBCK1) . Poor antibody responses to polysaccharides. HOIP deficiency. HOIP1 (RNF31) . Lymphangiectasia. <i>Ig</i> : decreased. Calcium Channel Defects. Autoimmunity, EDA, non-progressive myopathy. <i>Ig</i> and Bc: NI. Tc: Normal, defective TCR mediated activation. ORAI-1 deficiency. ORAI1 . STIM1 deficiency. STIM1 Hennekam-lymphangiectasia-lymphedema syndrome. CCBE1 . Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features. <i>Ig</i> : decreased. Bc and Tc: Variable. STAT5b deficiency. STAT5B . Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity. Kabuki Sd. Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature, intellectual disability, congenital heart defects, recurrent infections (otitis media, pneumonia) in 50% of patients. Autoimmunity may be present. Low <i>IgA</i> and occasionally low <i>IgG</i> . KMT2D (MLL2) : AD. KDM6A : XL.

Fig. 2 (continued)

III. Predominantly Antibody deficiencies, a: Hypogammaglobulinemia

Serum Immunoglobulin Assays : IgG, IgA, IgM, IgE

IgG, IgA and/or IgM ↓↓

Exclude second causes: drugs [Hx], myeloma [bone marrow], lymphoma. Ig loss (not hypo-IgM) in urine, gastro-intestinal or skin.

→ B Lymphocyte (CD19+) enumeration (CMF)

B absent

Severe bacterial infection. All Ig isotypes decreased.

X-Linked Agammaglobulinemia. *BTX*.
Some patients have detectable Ig. ProBc: NI

AR : μ heavy chain Def. *IGHM*
Iga def. *CD79A*, IgB def. *CD79B*
BLNK def. *BLNK*, λ 5 def. *IGLL1*
ProBc: NI

PI3KR1 def. *PI3KR1*. ProBc: Decreased

AD
E47 transcription factor def. *TCF3*.

B >1 %

Commun Variable Immunodeficiency Phenotype

CVID with no gene defect specified.

Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease

AD. Severe bacterial infections; EBV susceptibility.
PIK3CD mutation (GOF). *PIK3CD* GOF. Decreased pro-Bc.
PIK3R1 deficiency (LOF). *PIK3CD*. Pro-Bc present and low memory Bc.

PTEN Deficiency (LOF). *PTEN*. AD. Lymphoproliferation, Autoimmunity.

CD19 deficiency. *CD19*. Recurrent infections, may have glomerulonephritis.

CD20 deficiency. *CD20*. Recurrent infections. Low IgG, NI or elevated IgM and IgA.

CD21 deficiency. Recurrent infections. Low IgG, impaired anti-pneumococcal response.

TRNT1 deficiency. *TRNT1*. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and hypogammag.

NFKB1 deficiency. *NFKB1*. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmunity, autoinflammation. Ig normal or low, Bc low or normal, low memory Bc.

NFKB2 deficiency. *NFKB2*. AD. Recurrent sinopulmonary infections, alopecia and endocrinopathies (ie, central adrenal insufficiency). Low Bc.

IKAROS deficiency. *IKZF1*. AD. Recurrent sinopulmonary infections. Low or normal Bc potentially reducing levels with age.

ATP6AP1 deficiency. *ATP6AP1*. XL. Hepatopathy, leukopenia, low copper. Leukopenia and hypogammag.

CD81 deficiency. *CD81*. Recurrent infections, may have glomerulonephritis.

TACI deficiency. *TNFRSF13B* (*TACI*). AD or AR. Variable clinical expression

BAFF receptor deficiency. *TNFRSF13C* (*BAFF-R*). Variable clinical expression. Low IgG and IgM.

TWEAK deficiency. *TWEAK* (*TNFSF12*). AD. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody.

Mannosyl-oligosaccharide glucosidase deficiency (MOGS). *MOGS* (*GCS1*). Bacterial and viral infections, severe neurologic disease, also known as congenital disorder of glycosylation type IIb (CDG-IIb). Severe hypogammag.

TTC37 deficiency. *TTC37*. Recurrent bacterial and viral infections, Abnormal hair findings: trichorrhexis nodosa. Poor antibody response to pneumococcal vaccine.

IRF2BP2 deficiency. *IRF2BP2*. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulinemia, absent IgA.

III. Predominantly Antibody deficiencies. b: Other Antibody deficiencies

Serum Immunoglobulin Assays : IgG, IgA, IgM, IgE

Severe Reduction in Serum IgG and IgA with
NI/elevated IgM and Normal Numbers of Bc :
Hyper IgM Syndromes

AID deficiency. *AICDA*.

Bacterial infections, enlarged lymph nodes and germinal centers.

UNG deficiency. *UNG*.

Enlarged lymph nodes and germinal centers.

INO80. *INO80*.

Severe bacterial infections.

MSH6. *MSH6*.

Family or personal history of cancer. Variable IgG, defects, increased IgM in some, NI Bc, low switched memory Bc.

Isotype, Light Chain, or Functional Deficiencies with Generally NI Numbers of Bc

Selective IgA deficiency. *Unknown*.

Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies.

Transient hypogammaglobulinemia of infancy. *Unknown*.

Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased.

IgG subclass deficiency with IgA deficiency. *Unknown*.

Recurrent bacterial infections. Reduced IgA with decrease in one or more IgG subclass.

Isolated IgG subclass deficiency. *Unknown*.

Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections. Reduction in one or more IgG subclass.

Specific antibody deficiency with normal Ig levels and normal B cells. *Unknown*.

Reduced ability to produce antibodies to specific antigens. Ig: NI.

Ig heavy chain mutations and deletions.

Mutation or chromosomal deletion at 14q32.
May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.

Kappa chain deficiency. *IGKC*.

Asymptomatic. All immunoglobulins have lambda light chain.

Selective IgM deficiency. *Unknown*. Pneumococcal / bacterial infections. Absent serum IgM.

High Bc numbers due to constitutive NF- κ B activation

CARD11 GOF.

CARD11. AD. BENTA syndrome

Splenomegaly,
lymphadenopathy,
poor vaccine responses.

Fig. 3 Predominantly antibody deficiencies. **a** Hypogammaglobulinemias. **b** Other antibody deficiencies. AD: autosomal dominant transmission; AR: autosomal recessive transmission; Bc: B cells; BENTA: B cell expansion with NF- κ B and T cell anergy; CD: cluster of differentiation; CMF: flow cytometry; COPD: chronic obstructive pulmonary disease; def: deficiency; EBV: Epstein Barr virus; GOF: gain-of-function; Hx: patient history; Ig: immunoglobulins; NI: normal; XL: X-linked transmission

Compliance with Ethical Standards

IV. Diseases of immune dysregulation.			
a : Hemophagocytic Lymphohistiocytosis HLH & EBV susceptibility			
Hemophagocytic Lymphohistiocytosis (HLH)		Susceptibility to EBV	
Hypopigmentation: Partial albinism . Decreased NK and CTL activities (cytotoxicity and/or degranulation). Bc and Tc: NI	Familial Hemophagocytic Lymphohistiocytosis Syndromes: Fever, (H)SM, cytopenias, NI Bc. Increased activated Tc. Decreased to absent NK and CTL activities cytotoxicity.	RASGRP1 deficiency. RASGRP1. Recurrent pneumonia, herpes virus infections, EBV associated lymphoma. Increased IgA. Bc and Tc: Poor activation, proliferation, motility	EBV associated HLH
Chediak Higashi sd. LYST Recurrent infections, fever, (H)SM, bleeding tendency, progressive neurological dysfunction. Giant lysosomes (WBC), neutropenia, cytopenias, Specific hair shaft anomaly.	Perforin deficiency (FHL2). PRF1.	CD70 deficiency. CD70 (TNFSF7). Hodgkin's lymphoma. Reduced IgM, IgG, IgA (75%) and reduced Ag-specific Ab responses (50%). Bc: poor antibody and memory responses. Tc: low Treg, poor activation and function	XL, XLP1. SH2DIA. Clinical and immunologic features triggered by EBV infection: lymphoproliferation, Lymphoma. Hypogammaglobulinemia, Absent iNKT cells. Impaired NK cell and CTL cytotoxic activity . Reduced Memory B cells . SAP deficiency (CMF).
Griscelli sd type 2. RAB27a. Fever, (H)SM, cytopenias; Specific hair shaft anomaly.	UNC13D / Munc13-4 deficiency (FHL3). UNC13D.	CTPS1 deficiency. CTPS1. Recurrent/chronic bacterial and viral infections (EBV, VZV), EBV lymphoproliferation, Bc non-Hodgkin lymphoma. Tc: poor proliferation to Ag	XL, XLP2. XIAP. Splenomegaly, lymphoproliferation, Colitis, IBD, hepatitis. Hypogammaglobulinemia, Low iNKT cells. Increased T cells susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD). Normal NK and CTL cytotoxic activity. XIAP def (CMF)
Hermansky Pudlak sd type 2. AP3B1. Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia; Specific hair shaft anomaly.	Syntaxin 11 deficiency (FHL4). STX11.	ITK deficiency. ITK . EBV associated Bc lymphoproliferation, lymphoma, NI or low IgG. Tc: Progressive decrease	AR, CD27 deficiency . CD27 (TNFRSF7). Features triggered by EBV infection, aplastic anemia, low iNKTc lymphoma. Low Ig
Hermansky-Pudlak sd, type 10. AP3D1. Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay .	STXBP2 / Munc18-2 deficiency (FHL5) STXBP2. Enteropathy	MAGT1 deficiency (XMEN). MAGT1.XL. EBV infection, lymphoma, viral infections, respiratory and GI infections. Low CD4 Low recent thymic emigrant cells, poor proliferation to CD3	FAAP24 deficiency. FAAP24. EBV-driven lymphoproliferative disease. Failure to kill autologous EBV transformed Bc.
		PRKCD deficiency. PRKCD. Recurrent infections, EBV chronic infection, lymphoproliferation, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). Low IgG. Low memory Bc high CD5 Bc	

Fig. 4 Diseases of immune dysregulation. **a** Hemophagocytic lymphohistiocytosis. **b** Other diseases of immune dysregulation. Ab: antibody; AD: autosomal dominant transmission; Ag: antigen; ALPS: autoimmune lymphoproliferative syndrome; APS: autoimmune polyendocrinopathy syndrome; AR: autosomal recessive transmission; Bc: B cells; CD: cluster of differentiation; CMF: flow cytometry; CTL: cytotoxic T lymphocytes; def: deficiency; DNT: double negative T cells; EBV: Epstein

Barr virus; FHL: familial hemophagocytic lymphohistiocytosis; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; IBD: inflammatory bowel disease; Ig: immunoglobulin; IL-10: interleukin-10; LOF: loss-of-function; iNKT: invariant NKT cells; NK: natural killer cells; NI: normal; sd: syndrome; SLE: systemic lupus erythematosus disease; Tc: T cells; TCR: T cell receptor; XL: X-linked transmission

IV. Diseases of immune dysregulation. b: Sd with Autoimmunity and Others

Syndromes with Autoimmunity				Immune Dysregulation with Colitis:IBD, NI Tc & Bc	
Increased CD4 ⁺ CD8 ⁺ TCR α/β (double negative (DN) T cells) ?					
Yes	Occasionally	No: Regulatory T Cell Defects ?			
ALPS Autoimmune Lymphoproliferative Sd <i>Chronic adenopathy Splenomegaly, defective lymphocyte apoptosis.</i> ALPS-FAS. TNFRSF6. AD or AR. Autoimmune cytopenias, increased lymphoma risk, IgG and IgA NI or increased, elevated serum FasL, IL-10, vitamin B12. ALPS-FASLG. TNFSF6. AR. autoimmune cytopenias, SLE, soluble FasL is not elevated ALPS-Caspase10. CASP10. AD. ALPS-Caspase 8. CASP8. AR. Bacterial and viral infections, Hypogammaglobulinemia. Defective lymphocyte activation. Slightly increased DNT cells. FADD deficiency. FADD. AR. Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction.	LRBA deficiency. LRBA. AR. Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration, recurrent infections. Reduced IgG and IgA in most. Low or normal numbers of Bc. Normal or decreased CD4 numbers, Tc dysregulation. STAT3 GOF mutation. STAT3. AD. Lymphoproliferation, solid organ autoimmunity, recurrent infections. Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation and autoimmunity. Decreased Tregs and impaired function. Tc and Bc decreased.	No Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy: APECED (APS-1) . AIRE. AR/ AD. Hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia, enteropathy, pernicious anemia. ITCH deficiency. ITCH. AR. Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea/enteropathy, hepatitis, developmental delay, dysmorphic facial features . ZAP-70 combined hypomorphic and activation mutations. ZAP70. AR (LOF/GOF) Severe autoimmunity. Hyperactive Zap70 kinase. Decreased CD8. Tripeptidyl-Peptidase II Deficiency. TPP2. AR. Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections. Decreased Tc and Bc. JAK1 GOF. JAK1. AD GOF. HSM, eosinophilia, eosinophilic enteritis, thyroid disease, poor growth, viral infections. Prolidase deficiency. PEPD. AR. Auto-antibodies common, chronic skin ulcers, eczema, infections	Yes IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. FOXP3. Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, elevated IgE, IgA. Lack and/or impaired function of CD4 ⁺ CD25 ⁺ FOXP3 ⁺ regulatory T cells (Tregs). CD25 deficiency. IL2RA. AR. Lymphoproliferation, autoimmunity, impaired Tc proliferation. No CD4 ⁺ CD25 ⁺ cells with impaired function of Tregs cells. CTLA4 deficiency (ALPSV). CTLA4. AD. Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration recurrent infections . Impaired function of Tregs. Tc and Bc decreased. BACH2 deficiency. BACH2. AD. Lymphocytic colitis, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.	IL-10 deficiency. IL10. AR. Folliculitis, recurrent respiratory diseases, arthritis. No functional IL-10 secretion. IL-10Ra deficiency. IL10RA. AR. Folliculitis, recurrent respiratory diseases, arthritis, lymphoma. Leukocytes unresponsive to IL-10. IL-10Rb deficiency. IL10RB. AR. Folliculitis, recurrent respiratory diseases, arthritis, lymphoma. Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29 NFAT5 haploinsufficiency. NFAT5. AD. Recurrent Sinopulmonary infections. Decreased memory Bc and plasmablasts.	

Fig. 4 (continued)

Fig. 5 Congenital defects of phagocyte number, function, or both. **a** ▶ Neutropenia. **b** Functional defects of phagocytes. AD: autosomal dominant transmission; AML: acute myeloid leukemia; AR: autosomal recessive transmission; BCG: Bacillus Calmette-Guerin; CD: cluster of differentiation; CGD: chronic granulomatous disease; CMF: flow cytometry; CMMML: chronic myelomonocytic leukemia; def: deficiency; DHR: dihydrorhodamine-1,2,3; GOF: gain-of-function; IUGR: intrauterine growth retardation; MDS: myelodysplasia; NBT: nitroblue of tetrazolium; NK: natural killer cells; WBC: white blood cells; XL: X-linked transmission

V. Congenital defects of phagocyte number, function, or both. a : Neutropenia_(without anti-PMN)

Syndrome associated	No syndrome associated
Shwachman-Diamond syndrome. <i>SBDS</i>. AR. <i>DNAJC21</i>. AR. Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia	Elastase deficiency (SCN1). <i>ELANE</i>. AD. Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).
G6PC3 deficiency (SCN4). <i>G6PC3</i>. AR. Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O ₂ ⁻ production.	HAX1 deficiency (Kostmann Disease) (SCN3). <i>HAX1</i>. AR. Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
Glycogen storage disease type 1b. <i>G6PT1</i>. AR. Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.	GFI1 deficiency (SCN2). <i>GFI1</i>. AD. B/T lymphopenia
Cohen syndrome. <i>COH1</i>. AR. Dysmorphism, mental retardation, obesity, deafness.	X-linked neutropenia/ myelodysplasia WAS GOF. <i>WAS</i>. Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies .
Barth Syndrome (3-Methylglutaconic aciduria type II). <i>TAZ</i>. XL. Cardiomyopathy, myopathy, growth retardation.	G-CSF receptor deficiency. <i>CSF3R</i>. AR. Stress granulopoiesis disturbed
Clericuzio syndrome (Poikiloderma with neutropenia). <i>C16ORF57</i> (<i>USB1</i>). AR. Retinopathy, developmental delay, facial dysmorphism, poikiloderma.	Neutropenia with combined immune deficiency. <i>MLK1</i>. AR. Mild thrombocytopenia. Lymphopenia.
VPS45 deficiency (SCN5). <i>VPS45</i>. AR. Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.	
P14/LAMTOR2 deficiency. <i>LAMTOR2</i>. AR. Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.	
JAGN1 deficiency. <i>JAGN1</i>. AR. Osteopenia. Myeloid maturation arrest.	
3-Methylglutaconic aciduria. <i>CLPB</i>. AR. Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.	
SMARCD2 deficiency. <i>SMARCD2</i>. AR. Developmental aberrations, bones defect, myelodysplasia	
WDR1 deficiency. <i>WDR1</i>. AR. Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.	
HYOU1 deficiency. <i>HYOU1</i>. AR. Hypoglycemia, inflammatory complications.	

V. Congenital defects of phagocyte. b : Functional defects

Syndrome associated	No Syndrome associated: DHR assay (or NBT test)?
Cystic fibrosis. <i>CFTR</i>. AR. Pancreatic insufficiency, Respiratory infections, elevated sweat chloride	Normal
Papillon-Lefèvre . <i>CTSC</i>. Periodontitis, palmoplantar hyperkeratosis	Abnormal
Localized juvenile periodontitis . <i>FPR1</i>. Periodontitis only	GATA2 def (MonoMac sd) . <i>GATA2</i>, AD. Susceptibility to Mycobacteria, Papilloma Viruses, Histoplasmosis, Lymphedema. Pulmonary alveolar proteinosis, myelodysplasia/AML/ CMML . Monocytopenia. Low NK.
β-Actin . <i>ACTB</i> Mental retardation.	Specific granule deficiency. <i>C/EBPE</i>. Bilobed nuclei
Leukocyte adhesion deficiency. <i>Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000)</i> LAD I . <i>ITGB2</i> Delayed cord separation with omphalitis+++, no pus formation, lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. , CD18 def (CMF) severity of the disease correlates with the degree of deficiency in CD18. (WBC 20,000–150,000 with 60–85 % neutrophils) LAD II. <i>SLC35C1</i> Extremely rare. Recurrent infections. Severe growth delay and severe intellectual deficit. Facial dysmorphism (depressed nasal bridge). Severe periodontitis later in life. Bombay blood group. Infections: rarely life threatening. Patients may live to adulthood. LAD III. <i>FERMT3</i> Severe bacterial infections and severe bleeding disorder; osteopetrosis (severe cases). Platelet aggregation assay.	CGD. Early onset of severe and recurrent infections affecting initially the natural barriers of the organism (lungs, lymph nodes, skin), and eventually inner structures (liver, spleen, bones, brain, and +++ hepatic abscess). Autoinflammatory phenotype, IBD Granulomas obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn's like disease) and perianal disease : up to 30 % Pathogens : typically catalase positive bacteria (<i>S. aureus</i> and gram-negative bacilli, <i>Aspergillus</i> , <i>Candida</i>); other: <i>Burkholderia cepacia</i> , <i>Chromobacterium violaceum</i> , <i>Nocardia</i> , and invasive <i>Serratia marcescens</i> . In developing countries, BCG : adverse effects in up to 20 %. Microscopic granulomas. XL CGD: <i>CYBB</i> (gp91 ^{phox}) <i>NCF1</i> (p47 ^{phox}) , AR <i>CYBA</i> (p22 ^{phox}) , AR <i>NCF4</i> (p40 ^{phox}) , AR <i>NCF2</i> (p67 ^{phox}) , AR Rac 2 def . <i>RAC2</i>. Poor wound healing. LAD phenotype. G6PD def Class I. <i>G6PD</i>. Reduced DHR. Infections.
	Pulmonary alveolar proteinosis. <i>CSF2RA</i>, AR. <i>CSF2RB</i>, XL. Affected cells: Alveolar macrophages. Affected function: GM-CSF signaling

VI. Defects in Intrinsic and Innate immunity. a : Bacterial and Parasitic Infections

Predisposition to Invasive Bacterial infections (pyogens):	Predisposition to Parasitic and Fungal infections		Others
<p><i>meningitis, sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever.</i></p> <p>Predominant pathogens (<i>S. pneumoniae</i>, <i>S. aureus</i> and <i>Pseudomonas aeruginosa</i>). Non-invasive bacterial infections (skin infections and upper respiratory tract infections). Improve with age.</p> <p>Routine Usual screening tests are normal. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding) : available only in specialized clinical immunology laboratories.</p> <p>IRAK4 def. <i>IRAK4</i>, AR</p> <p>MyD88 def. <i>MYD88</i>, AR.</p> <p>IRAK-1 def. <i>IRAK1</i>, XL.</p> <p>X-linked MECP2 deficiency-related syndrome due to a large <i>de novo</i> Xq28 chromosomal deletion encompassing both <i>MECP2</i> and <i>IRAK1</i></p> <p>TIRAP def. <i>TIRAP</i>, AR.</p> <p>Staphylococcal disease during childhood.</p> <p>Isolated congenital asplenia.</p> <p>Bacteremia (encapsulated bacteria). No spleen.</p> <p>RPSA, AD</p> <p>HMOX, AR. Hemolysis, nephritis, inflammation</p>	<p>Predisposition to Mucocutaneous Candidiasis (CMC)</p> <p>Chronic Mucocutaneous Candidiasis without ectodermal dysplasia</p> <p>STAT1 GOF. <i>STAT1</i>, AD</p> <p>various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy</p> <p>IL-17F deficiency.</p> <p><i>IL17F</i>, AD. Folliculitis.</p> <p>IL-17RA deficiency.</p> <p><i>IL17RA</i>, AR</p> <p>Folliculitis. Susceptibility to <i>S. aureus</i> (skin infections)</p> <p>IL-17RC deficiency.</p> <p><i>IL17RC</i>, AR.</p> <p>ACT1 deficiency. <i>ACT1</i>, AR.</p> <p>Blepharitis, folliculitis and macroglossia.</p>	<p>CARD9 def. <i>CARD9</i>, AR.</p> <p>Predisposition to INVASIVE Fungal Diseases.</p> <p>Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections.</p> <p>Trypanosomiasis. <i>APOL1</i>, AD</p> <p>Inborn Errors of Immunity Related to Non-Hematopoietic Tissues</p>	<p>Osteopetrosis. <i>TNFRSF11A</i>, <i>PLEKHM1</i> AR.</p> <p><i>TCIRG1</i>, AR. + hypocalcemia</p> <p><i>CLCN7</i>, <i>OSTM1</i>, AR. + hypocalcemia, neurologic features</p> <p><i>SNX10</i>, AR. + visual impairment</p> <p><i>TNFSF11</i>, AR. + severe growth retardation</p> <p>Hydradenitis suppurativa. <i>PSENEN</i>, AD.</p> <p><i>NCSTN</i>, AD. + acne</p> <p><i>PSEN</i>, AD. + hyperpigmentation</p> <p>Acute liver failure due to NBAS def. <i>NBAS</i>, AR.</p> <p>Fever induces liver failure</p> <p>Acute necrotizing encephalopathy. <i>RANBP2</i>, AD.</p> <p>Fever induces acute encephalopathy</p>

Fig. 6 Defects in intrinsic and innate immunity. **a** Bacterial and parasitic infections. **b** MSMD and viral infection. AD: autosomal dominant transmission; AR: autosomal recessive transmission; BCG: Bacillus Calmette-Guerin; CD: cluster of differentiation; CMC: chronic mucocutaneous candidiasis; GOF: gain-of-function; IFNg: interferon-

gamma; HHV6: human herpes virus type 6; HPV: human papilloma virus; HSV: herpes simplex virus; LOF: loss-of-function; MSMD: Mendelian susceptibility to mycobacterial disease; NK: natural killer cells; RNA: ribonucleic acid; sd: syndrome; Tc: T cells; TLR3: Toll-like receptor type 3; VZV: varicella zoster virus; XL: X-linked transmission

VI. Defects in Intrinsic and Innate immunity. b : MSMD and Viral infection

Mendelian Susceptibility to mycobacterial disease (MSMD)		Predominant susceptibility to viral infection		
Severe phenotypes.	Moderate phenotypes.	Epidermodysplasia verruciformis (HPV)	Predisposition to Severe Viral Infection	Herpes simplex Encephalitis.
<p>Complete IFNGR1 Def and IFNGR2 Def. IFNGR1, IFNGR2. AR.</p> <p>Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes),</p> <p><i>Salmonella</i> spp., <i>Listeria monocytogenes</i> and viruses</p>	<p>With Susceptibility to <i>Salmonella</i></p> <p>IL-12 and IL-23 receptor b1 chain deficiency. IL12RB1. AR. IL-12p40 (IL-12 and IL-23) def. IL12B. AR.</p> <p>STAT1 LOF. STAT1(AD)</p> <p>Partial IFNγR1. IFNGR1. AR. Partial IFNγR2. IFNGR2. AR.</p> <p>AD IFNGR1. IFNGR1. AD. Mycobacterial osteomyelitis</p> <p>Tyk2 deficiency. TYK2. AR. Susceptibility to viruses, +/- elevated IgE. Multiple cytokine signaling defect.</p> <p>ISG15 Def. ISG15. AR. Brain calcification. IFNγ production defect.</p> <p>Macrophage gp91 phox deficiency. CYBB, XL IRF8 deficiency. IRF8 AD</p> <p>IRF8 deficiency. IRF8 AR Multiple other infectious agents. Myeloproliferation</p> <p>RORc deficiency. RORC AR. Susceptibility to <i>Candida</i>. IFNγ production defect, complete absence of IL-17A/F-producing Tc</p> <p>JAK1 (LOF). JAK1. AR. Susceptibility to viruses, urothelial carcinoma. IFNγ production.</p>	<p>EVER1 def. TMC6. AR.</p> <p>EVER2 def. TMC8. AR.</p> <p>WHIM (Warts, Hypogammaglobulinemia, infections, myelokathexis) sd. CXCR4 AD GOF.</p> <p>Warts (HPV) infection, neutropenia, low B cell number, hypogammaglobulinemia.</p>	<p>STAT1 Def (AR LOF). STAT1. (+ <i>Mycobacteria</i>)</p> <p>STAT2 deficiency. STAT2. AR. Disseminated vaccine-strain measles</p> <p>IRF7 deficiency. IRF7. AR. Severe influenza disease. Defect of IFN-α, β and γ production and IFN-λ production</p> <p>IFNAR2 deficiency. IFNAR2 AR. Disseminated vaccine-strain measles, HHV6. No response to IFN-α.</p> <p>CD16 deficiency. FCGR3A. AR. Severe herpes viral infections, particularly VZV, Epstein Barr virus (EBV), and HPV.</p> <p>MDA5 deficiency (LOF). IFIH1. AR. Rhinovirus and other RNA viruses</p>	<p>Dominant clinical phenotype is <i>Herpes simplex</i> encephalitis (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age. Incomplete clinical penetrance for all etiologies listed here.</p> <p>Routine screening tests are normal.</p> <p>Specific tests examining the TLR3 pathway : marked decrease in the ability of patient's fibroblasts to produce IFN-α and β in response to HSV1 infection.</p> <p>TLR3 (AD,AR), UNC93B1 (AR), TRAF3 (AD), TICAM1 (TRIF) (AR,AD), TBK1 (AD), IRF3 (AD).</p>

Fig. 6 (continued)

VIIa. Auto-inflammatory disorders		
Recurrent inflammation Recurrent fever	Systemic inflammation with urticaria rash	Others
<p>Familial Mediterranean Fever (FMF) *. <i>MEFV</i>. AR or AD</p> <p>DA: 1–4 days FA : Variable.</p> <p>Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis and inflammatory bowel disease Colchicine-responsive +++.</p>	<p>Familial Cold Autoinflammatory Syndrome (CAPS) *. <i>NLRP3, NLRP12</i>. AD GOF DA: 24–48H</p> <p>Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure.</p>	<p>CANDLE sd (chronic atypical neutrophilic dermatitis with lipodystrophy).</p> <p><i>PSMB8</i>, AR and AD. (Variants in <i>PSMB4</i>, <i>PSMB9</i>, <i>PSMA3</i>, and <i>POMP</i>) Contractures, panniculitis, ICC, fevers.</p>
<p>Mevalonate kinase def* (Hyper IgD sd). <i>MVK</i>. AR</p> <p>DA: 3–7 days FA: 1–2 monthly.</p> <p>Cervical adenopathy. Oral aphthosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.</p>	<p>Muckle Wells syndrome (CAPS) *. <i>NLRP3</i>. AD GOF.</p> <p>Ethnic group : North European</p> <p>Continuous fever. Often worse in the evenings. Deafness (SNHL), Conjunctivitis, Amyloidosis.</p>	<p>COPA defect. <i>COPA</i>. AD</p> <p>Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production</p>
<p>TNF receptor-associated periodic syndrome; TRAPS. <i>TNFRSF1A</i>. AD.</p> <p>DA: 1–4 weeks FA : Variable</p> <p>Prolonged fever. Serositis, rash, Periorbital edema and conjunctivitis; Amyloidosis. Joint inflammation.</p>	<p>Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) *. <i>NLRP3</i>. AD GOF.</p> <p>Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, Deforming arthropathy, Mental retardation. Sensorineural deafness. Visual loss.</p>	<p>NLR4-MAS (macrophage activating syndrome)*. <i>NLR4</i>.</p> <p>AD GOF.</p> <p>Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure.</p>
	<p>PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID*. <i>PLC2G</i>. AD GOF.</p> <p>Cold Urticaria. Autoimmunity. Blistering skin lesion, pulmonary and bowel disease. Hypogammaglobulinemia, autoinflammation.</p>	
	<p>NLRP1 deficiency*. <i>NLRP1</i>. AR.</p> <p>Dyskeratosis, autoimmunity and arthritis.</p>	
	<p>A20 haploinsufficiency. <i>TNFAIP3</i>. AD LOF. Early onset systemic inflammation, Arthralgia/arthritis, oral/genital ulcers, ocular inflammation.</p>	

Fig. 7 a, b Autoinflammatory disorders. *Diseases affecting the inflammasome. AD: autosomal dominant transmission; AR: autosomal recessive transmission; BSN: bilateral striatal necrosis; CAPS: cryopyrin-associated periodic syndrome; DA: duration of inflammation episode; FA: frequency of inflammation episode; FCL: familial chilblain lupus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis;

HSM: hepatosplenomegalia; ICC: intracranial calcifications; IL: interleukin; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; SMS: Singleton-Merten syndrome; SNHL: sensorineural hearing loss; SP: spastic paraparesis; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections

VIIb. Auto-inflammatory disorders

Sterile inflammation (skin / bone / joints)		Type 1 Interferonopathies
Predominant on the bone / joints	Predominant on the skin	<i>Progressive encephalopathy, ICC, Cerebral atrophy, HSM, leukodystrophy , Thrombocytopenia, Elevated hepatic transaminases . Chronic cerebrospinal fluid (CSF) lymphocytosis</i>
<p>Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzinemia and hypercalprotectinemia. <i>PSTPIP1 (C2BP1)</i>. AD</p> <p>DA: 5 days FA: Fixed interval : 4-6 weeks</p> <p>Sterile pyogenic arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks</p>	<p>Blau syndrome. <i>NOD2 (CARD15)</i>. AD. Continuous inflammation.</p> <p>Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response.</p> <p>CAMPS. <i>CARD14</i>. AD. Psoriasis.</p> <p>DITRA. (Deficiency of IL-36 receptor antagonist). <i>IL-36RN</i>. AR .</p> <p>Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis.</p> <p>ADAM17 deficiency. <i>ADAM17</i>. AR.</p> <p>Early-onset pustular dermatitis, short and broken hair, paronychia, frequent cutaneous bacterial infections, and Early onset diarrhea , high IL-1 and IL-6 production. Lack of TNF-α was considered partly responsible for their increased susceptibility to infection and development of cardiomyopathy.</p> <p>SLC29A3 mutation. <i>SLC29A3</i>. AR.</p> <p>Hyperpigmentation hypertrichosis, Rosai-Dorfman like histiocytosis-lymphadenopathy plus H syndrome</p> <p>Otulipenia/ORAS. <i>OTULIN</i>. AR.</p> <p>Arthralgia, Fever, diarrhea , dermatitis. Lipodystrophy, myalgia, Neutrophilia</p> <p>AP1S3 deficiency. <i>AP1S3</i>. AR.</p> <p>Pustular psoriasis</p>	<p>Aicardi-Goutieres syndrome. <i>TREX1</i> AR-AD (+SLE, FCL), <i>RNASEH2A, RNASEH2B</i> (+SP), <i>RNASEH2C, SAMHD1</i> (+ Skin vascularitis, mouth ulcers, arthropathy, FCL), <i>ADAR1</i> (+BSN, SP), <i>IFIH1</i> GOF AD (+ SLE, SP, SMS)</p> <p>Spondyloenchondro-dysplasia with immune dysregulation (SPENCD). <i>ACPS5</i>.</p> <p>Possibly recurrent bacterial and viral infections, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, short stature, SP, ICC.</p> <p>STING-associated vasculopathy, infantile-onset. <i>TMEM173</i>. Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL.</p> <p>ADA2 deficiency. <i>CECR1</i>. Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, low IgM, Hypogammagl, Lymphopenia</p> <p>XL reticulate pigmentary disorder. <i>POLA1</i>. Hyperpigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies</p> <p>USP18 def . <i>USP18</i>. TORCH like syndrome.</p>

Fig. 7 (continued)

VIII. Complement deficiencies				
Susceptibility to infections				
High		Low		
Disseminated Neisserial infections	Recurrent pyogenic infections	SLE-like syndrome. Infections with encapsulated organisms Absent CH50 hemolytic activity	Atypical Hemolytic Uremic Syndrome	Others
Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity.	Normal CH50. Absent AH50 hemolytic activity	C1q def. C1QA, C1QB, C1QC.	C3 GOF. C3. AD. Infections, glomerulonephritis. Increased activation of complement	C1 inhibitor. SERPING1. AD, Hereditary angioedema. Spontaneous activation of the complement pathway with consumption of C4/C2
C5 def. C5	Properdin def. PFC. XL	C1r def. C1R. Ehlers Danlos phenotype	Factor B GOF. CFB. AD. Increased spontaneous AH50	Membrane Attack Complex Inhibitor deficiency. CD59. Hemolytic anemia. Polyneuropathy.
C6 def. C6	Factor D def. CFD. AR.	C1s def. C1S. Multiple autoimmune diseases; Ehlers Danlos phenotype	Factor H def. CFH. AR or AD. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3	CD55 deficiency (CHAPLE disease). CD55. AR. Protein losing enteropathy, thrombosis
C7 def. C7. + Vasculitis		C2 def. C2. Vasculitis, Polymyositis, atherosclerosis	Factor H-related protein deficiencies. CFHR1-5. AR or AD. Later onset, disseminated neisserial infections. Normal CH50, AH50, autoantibodies to Factor H.	
C8 def. C8A, C8B, C8G	Ficolin 3 def. FCN3. AR. Infections mainly in the lungs; abscesses, necrotizing enterocolitis in infancy; selective antibody defect to Pneumococcal polysaccharides. Absence of complement activation by the Ficolin 3 pathway	C4 def. C4A, C4B. AR. Partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense	Factor I deficiency. AR. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3	
C9 def. C9. Mild susceptibility.	Factor B. CFB LOF. AR. Infections with encapsulated organisms. Deficient activation of the alternative pathway		Thrombomodulin def. THBD. AD. Normal CH50, AH50	
			Membrane Cofactor Protein deficiency. CD46. AD, Glomerulonephritis. Infections, preeclampsia. Inhibitor of complement alternate pathway, decreased C3b binding	

Fig. 8 Complement deficiencies. AD: autosomal dominant transmission; AH50: alternate pathway hemolytic activity; AR: autosomal recessive transmission; CH50: complement hemolytic activity; def: deficiency;

LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; XL: X-linked transmission

Fig. 9 Phenocopies of PID. ALPS: autoimmune lymphoproliferative syndrome; AutoAb: auto-antibodies; CID: combined immunodeficiency; CMC: chronic mucocutaneous candidiasis; GOF: gain-of-function; MSMD: Mendelian susceptibility to mycobacterial disease; PRCA: pure red cell aplasia

IX. Phenocopies of PID	
Associated with Somatic Mutations	Associated with Auto-Antibodies
<i>Splenomegaly, lymphadenopathy, autoimmune cytopenias. Defective lymphocyte apoptosis.</i> ALPS-SFAS. (somatic mutations in <i>TNFRSF6</i>)// <i>ALPS-FAS</i> (ALPS type Im) RALD. RAS-associated autoimmune leukoproliferative disease. (ALPS Like); N-RAS GOF, K-RAS GOF Sporadic; granulocytosis, monocytosis/ALPS-like	Chronic mucocutaneous candidiasis (isolated or with APECED syndrome). AutoAb to IL-17 and/or IL-22. Endocrinopathy, chronic mucocutaneous candidiasis /CMC. Germline mutation in <i>AIRE</i>
Cryopyrinopathy , (Muckle-Wells /CINCA/NOMID-like syndrome). NLRP3. Urticaria-like rash, arthropathy, neurological symptoms	Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNγ. Mycobacterial, fungal, salmonella, VZV infections / MSMD or CID.
Hypereosinophilic syndrome due to somatic mutations in STAT5b. STAT5b. GOF. Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.	Recurrent skin infection. AutoAb to IL-6. Staphylococcal infections / <i>STAT3</i> deficiency
	Pulmonary alveolar proteinosis . AutoAb to GM-CSF. Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis/CSF2RA deficiency
	Acquired angioedema . AutoAb to C1 inhibitor. Angioedema /C1 inhibitor deficiency
	Atypical Hemolytic Uremic Syndrome . AutoAb to Factor H. Spontaneous activation of the alternative complement pathway
	Thymoma with hypogammaglobulinemia (Good syndrome). AutoAb to various cytokines. Invasive bacterial, viral or opportunistic infections, autoimmunity, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea. No B cells.

Conflict of Interest The authors declare that they have no conflict of interest.

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